We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Stem Cell Transplantation in Chronic Lymphocytic Leukemia

Anna Gazzola, Alessandro Broccoli,
Vittorio Stefoni and Pier Paolo Piccaluga

Additional information is available at the end of the chapter

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia diagnosed in Western world, with an incidence of $3–6/10^5$ per year, that increase to $12.8/10^5$ at the age of 65 [1-3]. This disease is characterized by an extremely heterogeneous behavior, with the clinical course varying from patients who never require therapy to patients with a rapid disease progression and early resistance to treatment. In fact, about 20% of the patients show an aggressive course and die within few years from diagnosis [3, 4].

Molecular markers, such as cytogenetic alteration [5], immunoglobulin heavy chain (*IGH*) and *TP53* genes mutational status [6, 7], zeta associated protein 70 (ZAP70) expression [8] and CD38 expression [9], help to predict outcomes in CLL. However, their presence in the absence of clinical symptomatology is not a sufficient criterium to initiate therapy. Further, even in the absence of these factors, resistance to purine-analogue treatment can occur. This suggests that additional molecular mechanisms, which confer drug refractoriness in poor-risk CLL, do exist. In this regard, based on next generation sequencing studies, it was recently shown that additional genetic events can predict CLL patients outcome, including *NOTCH1*, *SF3B1*, and *BIRC3* mutations [10-15].

A major issue in CLL is the identification of the optimal timing and type of first-line treatment. In the current recommendation of International Workshop on CLL (IWCLL) updated guidelines for the diagnosis and treatment of CLL the therapy is reserved for advanced, symptomatic or progressive disease [16]. Numerous studies showed that, either as first-line therapy or in relapsed/refractory settings, treatment with new agents, such as alemuzumab, ofatumumab, lenalidomide, and flavoperidole [17-22] or combination of conventional che-

motherapy to target immunotherapy lead to a better response in these patients [23-29]. These approaches significantly reduce the tumor load in refractory patients, even if the ultimate cure of disease has not yet been achieved. Therefore, CLL remains incurable outside the setting of allogeneic stem cell transplant (allo-SCT). In fact, up to date this is the only therapeutical approach that can potentially offer a curable solution to this disease [9]. The indications for SCT in CLL were established by European Bone Marrow Transplant (EBMT) [30]. Specifically, based on the evidence of efficacy and potential toxicity of SCT in CLL, these procedure is designated for high-risk CLL patents. These include: a) patients with *TP53* abnormalities, who fail to achieve complete remission (CR) or who progress within 12 months after purine analogues, b) those who relapse within 24 months after having achieved a response with purine-analogue-based combination therapy, c) those who relapsed after prior autologous SCT and d) patients who are fludarabine refractory [31, 32]. It should be noted that none of these categories requires assessment of biologic risk factors except cytogenetic detection of *TP53* deletions. Ongoing prospective clinical studies will determine the impact of biomarkers such as *IGH* mutational status and other cytogenetic abnormalities in identification of patients at sufficiently high risk for allogeneic SCT use at first CR. Several groups agree that allogeneic transplant early in the disease course is the best strategy for patients with high-risk or poor response to initial therapy. For those with durable first remissions, the timing of transplant is more controversial. The debate in "*when to proceed to a more aggressive treatment approach?*" in CLL is in part driven by the presence of new therapeutic strategies available for these patients. However, it is unknown how these therapies will change the indications for or the outcome following transplant in CLL. Nevertheless, these promising results have already started to impact the transplant recommendations in CLL patients in a similar manner to chronic myeloid leukemia (CML) patients in imatinib era.

In this chapter the Authors, based on their own experience as well as on the most updated literature, discuss the usage of autologous and allogeneic SCT in the clinical setting of CLL, also in the light of the novel biological prognostic indicators.

2. Autologous hematopoietic stem cell transplantation

Autologous stem cell transplantation (ASCT) has been extensively investigated as a treatment option for CLL patients during the last years.

Evidences from clinical and minimal residual disease (MRD) studies have suggested that ASCT has curative potential in only few patients. Nevertheless, ASCT might be capable of prolonged disease control even in CLL with poor-risk features.

Autologous transplantation consists in the collection of stem cells from the patient's marrow or peripheral blood before high-dose irradiation or chemotherapy and their subsequent reinfusion to guarantee a new blood production. The main problems with this procedure are the risk of re-infusion of leukemic cells that could potentially contaminate the stem cell population and the difficulty in mobilizing progenitor cell in patients who have received multiple previous treatments [33, 34]; particularly if purine analogs, have been administrated [35]. In addition,

the outcome of ASCT is strongly correlated with the status of the disease: patients transplant-ed in CR have a much better outcome than those transplanted with active disease [36]. There-fore, optimal disease control prior to transplantation is mandatory [33, 34, 37].

Other factors that negatively influence the transplantation outcome and correlate with early relapse are: the interval between the diagnosis and the transplant, the number of prior lines of therapy, the presence of adverse cytogenetic abnormalities and of unmutated *IGH* genes [36, 38]. In addition, the detection of MRD by either polymerase chain reaction (PCR) or flow cytometry after transplantation anticipates clinical relapse [39, 40].

As mentioned above, different studies have investigated the role of ASCT in patients with CLL and the results were controversial. A retrospective matched-pair analysis suggested a survival advantage for ASCT in 66 patients who had undergone a uniform high dose thera-py and transplantation over conventional therapy in 291 patients. With an overall median follow-up time of 70 and 86 months, survival was significantly longer for the patients who had undergone ASCT compared with conventionally treated patients [41]. However, in 2011, several prospective studies have failed to confirm the survival advantage of ASCT in advanced CLL patients [42, 43]. Brion et al. [43] published the results of a prospective multi-center randomized trial on the benefit of ASCT using a cyclophosphamide/TBI preparative regimen in advanced clinical-stage untreated CLL compared to conventional treatment. The conventional treatment was represented by 6 cicles of miniCHOP; for the ASCT cohort the scheduled therapy consisted of 3 miniCHOP cicles followed by immediate ASCT for pa-tients with a very good partial remission (VGPR) or CR. This study highlights the absence of differences in median overall survival (OS) between the two groups thus denying the supe-riority of ASCT over conventional therapy.

The necessity of additional randomized studies to better clarify the role of ASCT in the man-agement of patients with CLL was further emphasized by a comparative study conducted by the EBMT group in which 621 autografted patients were compared to 630 non-autograft-ed patients. Patients autografted within 18 months of diagnosis had a better outcome that those treated with chemotherapy, but this was offset by an inferior outcome of patients au-tografted after 18 months [44]. In addition it was found a promising benefit by the T-cell mediated cytotoxicity via autologous transplantation in the high-risk CLL population.

Interestingly, Porter et al. [45] reported on the management of a chemo-refractory, CLL pa-tient with del(17p) treated with autologous T-cells genetically modified to express anti-CD19; although the long-term disease control and late toxicities are not yet known, the patient was in remission [45].

Most of the studies published have relatively short follow up and therefore only focus on treatment related mortality (TRM) early after transplant, but the late consequences, particu-larly the development of secondary myelodysplasia and acute myeloid leukaemia (MDS/ AML), deserve some concern [37]. In fact, among 65 patients treated with fludarabine fol-lowed by ASCT, 8 developed MDS/ AML [37, 46]. Of note, in most studies, despite a high initial CR rate, relapse is common, suggesting that autologous transplant is unlikely to be curative in CLL [37]. However, based on the present literature, although ASCT cannot be

considered as a standard treatment it should be considered in the context of clinical trials or as an innovative therapy to prolong survival in selected patients (i.e. those with chemosensitivity, absence of unfavorable factors, and transplanted early in the course of the disease).

3. Allogeneic hematopoietic stem cell transplantation

In recent years, allogeneic hematopoietic stem cell transplant (allo-SCT) was visibly emerged as the favorite treatment option for patients with high-risk CLL. In fact, in contrast with ASCT, allo-SCT can induce durable responses even in patients refractory to therapy [47-49]. Studies on the outcomes post ASCT failed to show a plateau effect on survival curves and resulted in a remarkably high incidence of secondary myelodysplastic syndromes (9% to 12%) [50]. On the contrary, in most series where allo-SCT has been carried out, a plateau is observed, with 40–60% of the patients remaining alive and free of disease 5–6 years after transplantation [39, 44, 46, 48, 49, 51-55]. Therefore, allo-SCT become, in the last two decades, the first treatment approach with curative potential in CLL.

The crucial anti-leukemic principle of allo-SCT in CLL appears to be the graft-versus-leukemia effect (GVL). The resultant GVL effect derived from alloreactive donor T cells is the key mechanism responsible for lowering relapse rates after allo-SCT. There is evidence that the GVL effect plays an essential role in controlling the disease and reverts poor prognostic biological variables such as unmutated *IGH* genes [56, 57]. In addition, one of the most important advantage of allo-SCT includes infusion of tumor-free hematopoietic progenitor and effector cells from healthy donors. Of note, it is important to exclude the presence in donor peripheral blood of a monoclonal population immunophenotypically identical to that of patients with CLL; in fact it was demonstrated that CLL clones were found in around 12% of the first-degree relatives of patients with CLL and in up to 3% of the general population [58]. Nevertheless, the use of allo-SCT is limited due to the advanced age of most patients with CLL and the high mortality associated with the procedure (in the range 24–47%), main causes for death being graft-vs host disease (GVHD) and infections.

At present, ongoing prospective clinical studies will determine the impact of biomarkers including *IGH* mutational status and other cytogenetic abnormalities in identification of patients with sufficiently high risk to deserve use of allo-SCT in first CR.

4. Myeloablative allogeneic stem cell transplantation

In myeloablative allo-SCT, patients are given extremely high doses of chemotherapy, with or without radiation, to wipe out, or "ablate," the marrow. Then they are given an infusion of donor stem cells to revive blood cell production and immunity.

Several theoretical advantages of myeloablative allo-SCT over ASCT are: a) none tumor contamination of the stem cell b) GVL effect to eliminate chemotherapy-resistant leukaemia

cells by immune mechanisms c) better survival curves. In fact, studies from MD Anderson Cancer Center demonstrate improved outcome after allogeneic compared to ASCT [59] suggesting that myeloablative allo-SCT can induce durable remission even in patients with refractory disease. However, the major limitation of using myeloablative allo-SCT is the increased risk of transplant-associated morbidity and mortality, mostly from organ failure due to direct toxicity of the preparative regimen and/or development of GVHD [48, 60, 61].

Registry data from the International Bone Marrow Transplant Research (IBMTR) group and the EBMT group reported a transplant-related mortality (TRM) of 46% with mortality from GVHD of 20% [60]. These published data showed that approximately two-thirds of allo-transplanted CLL patients will succumb either to TRM or to recurrent disease, and approximately one-third will be cured of their disease [54, 60].

Active chronic GVHD is principal determinant of long-term morbidity and significantly reduced long-term health status in patients allografted for various hematological malignancies [62]. Indeed, transplant-related long-term morbidity after allo-SCT for CLL can be significant but is mainly restricted to those patients who have ongoing active chronic GVHD. However, in the majority of affected patients clinical symptoms of chronic GVHD resolved over time, allowing discontinuation of systemic therapeutic immunosuppression after a median of 25 months [63]. Further, a high graft rejection rates remain a relevant complication in myeloablative allo-SCT; a possible explanations could be the significant marrow infiltration in CLL patients at the time of transplantation, inversely correlated with outcome [64], and the role played by host dendritic cells, which are seriously defective in CLL patients [65]. Another problem is represented by the high infection rates, that correlated with preexisting immunosuppression. Infections are the cause of about 50% of all CLL-related deaths [62, 66] primarily in fludarabine and/or alemtuzumab-refractory patients [16, 67]. Moreover in recent reports the risk of infections has been clearly correlated with presence of GVHD [57, 63, 65, 68] and refractory disease [67, 69]. In addition, it is important to note that patients with chemosensitive disease have significantly better outcomes than patients with refractory disease, suggesting that an earlier application of allo-SCT may further improve transplantation outcomes [60, 70, 71].

In conclusion, allo-SCT is a therapy with curative potential in CLL and, in contrast to conventional treatment, with an high potential of providing long-term disease control even in patients with a very unfavorable biological and clinical risk profile. However, in addition to the disease risk, it is necessary to consider patient-related risk factors, such as age and co-morbidity, when allo-SCT is performed [63].

5. Reduced-intensity conditioning stem cell transplantation (nonmyeloablative allo-SCT)

Although myeloablative allo-SCT in CLL can result in durable remissions, rates of TRM are after unacceptably and greatly reduced its application, even in the most refractory and high-risk individuals.

Reduced-intensity conditioning (RIC) regimens were introduced as a way to take advantage of GVL effect, reducing TRM and making transplant more approachable also in older or younger patients with comorbidities [72, 73]. These reduced regimens, are associated with improved TRM; in fact, in 2003, the EBMT reported outcomes of 77 CLL patients who received an allo-SCT [74]. The authors described an encouraging TRM rate of 18%, an impressive overall response rate of 91%, as well as a 69% complete response rate and a 22% partial response rate, associated with reduction in the ablative intensity of the preparative regimen. This lower TRM (18%), when compared with that linked to a myeloablative conditioning (46%), turned out to be extremely promising [74].

On the contrary, there were no significant differences in terms of OS or progression free survival (PFS) between these two groups [74]. In fact, although nonmyeloablative transplants may carry a stronger safety profile, the rate of relapse was higher than that associated with traditional myeloablative treatment [74]. Interestingly, instead, Sorror et al. have recently published data indicating that non-myeloablative transplants can provide a lower risk of relapse [63]. They reported encouraging long-term outcomes in 82 CLL patients who received RIC allo-SCT. In this study, at a median follow-up of 5 years, TRM, PFS, and OS were 23%, 39%, and 50%, respectively, suggesting a curative potential for RIC allo-SCT in patients with relapsed CLL, with a more favorable toxicity profile particularly in older patients who would not have been eligible to receive myeloablative conditioning regimens [63].

In contrast to ASCT where the efficacy relies exclusively on the cytotoxicity administered with the high-dose regimen, and in agreement to myeloablative allo-SCT, nonmyeloablative allo-SCT adds the immune-mediated anti-host activities conferred with the graft as a second fundamental principle of antileukemic efficacy: the GVL effect.

There is no doubt that the main therapeutic principle of allo-SCT in CLL is GVL activity and this evidence derives from some remarkable observations such as: 1) decreasing relapse incidence over time even in RIC allo-SCT, in contrast to ASCT or other intensive therapies [56, 60, 63, 70, 71, 75, 76], 2) durable clinical and molecular responses due to antitumor activity [77], 3) reduced relapse rates in patients with chronic GVHD [78], 4) increased relapse rates associated with T cell–depleted grafts [79, 80], 5) high efficacy of donor lymphocyte infusions (DLIs) in the post-transplant relapse [65, 80].

This finging supports alloreactivity as the principal mechanism responsible for GVL.

On the other hand, the most important cause of RIC allo-SCT failure in CLL patients is the disease relapse. Early relapses are correlated with chemorefractory disease at the time of transplantation, the most of time due to the unsuccessfulness of RIC regimens in controlling the disease before the GVL effect. The late relapse, instead, derives from different mechanism including: CLL clonal evolution, development of tolerance [80], presence of tumor cells in "GVCLL sanctuary sites"[63] and an insufficient GVL effect to produce a complete disease eradication. Interestingly, an high percentage of these late relapses occurred in lymph nodes without bone marrow or peripheral blood involvement, or even in patients with MRD negative status [40, 53, 55, 81, 82].

Quantitative MRD monitoring by RQ-PCR or flowcytometry is an essential tool to establish the clinical benefit of allo-SCT in CLL; in fact, the absence of detectable MRD, one year after allo-SCT, was strongly associated with a reduced risk of clinical relapse. In addition, there are evidences of a powerful correlation between MRD status and GVL activity, while its direct involvement for guiding GVL-inducing immunomodulation needs further evaluation [83]. Therefore quantitative MRD monitoring seems to be mandatory to assure safe and effective immunotherapy in the context of allo-SCT [83].

The best approach to post transplant immunotherapy in CLL includes monoclonal antibody (MoAbs). Some of them, although a still short follow-up, show very promising results and the use of MoAbs in the conditioning or just after transplant, could improve the results of allo-SCT. Initially, RIC allo-SCT was associated with the use of only fludarabine and cyclophosphamide. The CLL3X trial from the German CLL Study Group evaluated the long-term outcome of RIC allo-SCT in patients with poor-risk CLL who received allogeneic transplant following fludarabine and cyclophosphamide-based conditioning. The 4-year non relapse mortality (NRM), event-free survival (EFS), and OS were 23%, 42%, and 65%, respectively. To improve relapse-free survival following transplant and to modulate the impact of GVHD, MoAbs have been incorporated into transplant regimens [84]. Alemtuzumab, Rituximab are the most used MoAbs with recognized clinical activity in CLL. Alemtuzumab is a humanized anti-CD52 IgG1 MoAb with an activity in reducing the incidence of GVHD but, also, associated with an high risk of death from opportunistic infections [85]. Rituximab (anti-CD20 MoAb), instead, used in tandem with RIC preparative regimens, can induce response and help in disease control, decreasing the incidence of acute GVHD and modulating the GVL effect. [59]. However, there is no clear consensus concerning the optimal conditioning regimen to be used prior to allo-HCT. Using RIC regimens may reduce toxic deaths, but the success of non-myeloablative allo-SCT is highly dependent on the chemosensitivity of the disease.

6. Conclusion and future directions

Despite much progress in its treatment, CLL continues to be an incurable disease with standard treatments. SCT cell transplantation has changed the management of CLL patients with refractory disease or younger patients with aggressive disease. In particular, ASCT has partially failed in the treatment of advanced CLL: it prolongs survival in selected patients, but unfortunately do not cure the disease. In addition, secondary MDS/AML is one of major complication in autografted patients.

Allo-SCT, conversely, may be an acceptable option: myeloablative allo-SCT is an opportunity for younger patients with bulky, refractory, or aggressive disease; RIC allo-SCT, instead, is an emerging curative possibility for older patients with high-risk disease.

Although allo-SCT appears to result in high response rates and eradication of PCR detectable MRD, the follow up of most clinical trials is too short to assess whether allo-SCT can cure CLL.

Future approaches in menagment of CLL must take in consideration the balance between increased morbidity and mortality of SCT in CLL with the potentiality of new therapy in the setting of the improvements in outcome.

In the absence of any other treatment modalities currently capable of improving outcome in CLL, SCT should be considered the main option for patients with high-risk, refractory to standard therapy or with relapsed after prior ASCT.

Author details

Anna Gazzola, Alessandro Broccoli, Vittorio Stefoni and Pier Paolo Piccaluga

*Address all correspondence to: pierpaolo.piccaluga@unibo.it

Hematopathology and Hematology Sections, Department of Hematology and Oncology "L. and A. Seràgnoli", S. Orsola-Malpighi Hospital, University of Bologna, Italy

References

[1] O'Brien S, del Giglio A, Keating M. Advances in the biology and treatment of B-cell chronic lymphocytic leukemia. Blood 1995;85(2):307-18.

[2] Rozman C, Montserrat E. Chronic lymphocytic leukemia. The New England journal of medicine 1995;333(16):1052-7.

[3] Muller-Hermelink, Montserrat, Catovsky, Campo, Harris, Stein. Chronic lymphocytic leukaemia/small lymphocytic lymphoma. In: Swerdlow SH, Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J., Vardiman, J.W, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues,. Lion: IARC; 2008:180-2.

[4] Dighiero G. Unsolved issues in CLL biology and management. Leukemia 2003;17(12):2385-91.

[5] Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. The New England journal of medicine 2000;343(26): 1910-6.

[6] Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. Blood 1999;94(6): 1840-7.

[7] Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol 2010;28(29):4473-9.

[8]   Rassenti LZ, Huynh L, Toy TL, et al. ZAP-70 compared with immunoglobulin heavy-chain gene mutation status as a predictor of disease progression in chronic lympho-cytic leukemia. The New England journal of medicine 2004;351(9):893-901.

[9]   Rassenti LZ, Jain S, Keating MJ, et al. Relative value of ZAP-70, CD38, and immuno-globulin mutation status in predicting aggressive disease in chronic lymphocytic leu-kemia. Blood 2008;112(5):1923-30.

[10] Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recur-rent mutations in chronic lymphocytic leukaemia. Nature 2011;475(7354):101-5.

[11] Fabbri G, Rasi S, Rossi D, et al. Analysis of the chronic lymphocytic leukemia coding genome: role of NOTCH1 mutational activation. The Journal of experimental medi-cine 2011;208(7):1389-401.

[12] Quesada V, Conde L, Villamor N, et al. Exome sequencing identifies recurrent muta-tions of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. Nature ge-netics 2011;44(1):47-52.

[13] Rossi D, Bruscaggin A, Spina V, et al. Mutations of the SF3B1 splicing factor in chron-ic lymphocytic leukemia: association with progression and fludarabine-refractori-ness. Blood 2011;118(26):6904-8.

[14] Rossi D, Rasi S, Fabbri G, et al. Mutations of NOTCH1 are an independent predictor of survival in chronic lymphocytic leukemia. Blood 2012;119(2):521-9.

[15] Rossi D, Fangazio M, Rasi S, et al. Disruption of BIRC3 associates with fludarabine chemorefractoriness in TP53 wild-type chronic lymphocytic leukemia. Blood 2012;119(12):2854-62.

[16] Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111(12):5446-56.

[17] Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103(9):3278-81.

[18] Moreton P, Kennedy B, Lucas G, et al. Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with pro-longed survival. J Clin Oncol 2005;23(13):2971-9.

[19] Stilgenbauer S, Zenz T, Winkler D, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker anal-yses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2009;27(24):3994-4001.

[20] Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immuno-therapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28(10):1749-55.

[21] Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial re-missions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111(11):5291-7.

[22] Phelps MA, Lin TS, Johnson AJ, et al. Clinical response and pharmacokinetics from a phase 1 study of an active dosing schedule of flavopiridol in relapsed chronic lym-phocytic leukemia. Blood 2009;113(12):2637-45.

[23] Tam CS, O'Brien S, Wierda W, et al. Long-term results of the fludarabine, cyclophos-phamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112(4):975-80.

[24] Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentos-tatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 2007;109(2):405-11.

[25] Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzu-mab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial. J Clin Oncol 2005;23(28):7024-31.

[26] Wierda W, O'Brien S, Wen S, et al. Chemoimmunotherapy with fludarabine, cyclo-phosphamide, and rituximab for relapsed and refractory chronic lymphocytic leuke-mia. J Clin Oncol 2005;23(18):4070-8.

[27] Lamanna N, Kalaycio M, Maslak P, et al. Pentostatin, cyclophosphamide, and rituxi-mab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia. J Clin Oncol 2006;24(10):1575-81.

[28] Flinn IW, Neuberg DS, Grever MR, et al. Phase III trial of fludarabine plus cyclophos-phamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia: US Intergroup Trial E2997. J Clin Oncol 2007;25(7):793-8.

[29] Catovsky D, Richards S, Matutes E, et al. Assessment of fludarabine plus cyclophos-phamide for patients with chronic lymphocytic leukaemia (the LRF CLL4 Trial): a randomised controlled trial. Lancet 2007;370(9583):230-9.

[30] Dreger P, Corradini P, Kimby E, et al. Indications for allogeneic stem cell transplanta-tion in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia 2007;21(1):12-7.

[31] Dreger P, Brand R, Michallet M. Autologous stem cell transplantation for chronic lymphocytic leukemia. Seminars in hematology 2007;44(4):246-51.

[32] Gribben JG. Stem-cell transplantation in chronic lymphocytic leukaemia. Best prac-tice & research 2007;20(3):513-27.

[33] Paneesha S, Milligan DW. Stem cell transplantation for chronic lymphocytic leukaemia. British journal of haematology 2005;128(2):145-52.

[34] Montserrat E. Role of auto- and allotransplantation in B-cell chronic lymphocytic leukemia. Hematology/oncology clinics of North America 2004;18(4):915-26, x.

[35] Tournilhac O, Cazin B, Lepretre S, et al. Impact of frontline fludarabine and cyclophosphamide combined treatment on peripheral blood stem cell mobilization in B-cell chronic lymphocytic leukemia. Blood 2004;103(1):363-5.

[36] Dreger P, van Biezen A, Brand R, et al. Prognostic factors for survival after autologous stem cell transplantation for chronic lymphocytic leukemia: the EBMT experience [abstract].. Blood 2002;96((Suppl. 1)):482a.

[37] Milligan DW, Fernandes S, Dasgupta R, et al. Results of the MRC pilot study show autografting for younger patients with chronic lymphocytic leukemia is safe and achieves a high percentage of molecular responses. Blood 2005;105(1):397-404.

[38] Ritgen M, Lange A, Stilgenbauer S, et al. Unmutated immunoglobulin variable heavy-chain gene status remains an adverse prognostic factor after autologous stem cell transplantation for chronic lymphocytic leukemia. Blood 2003;101(5):2049-53.

[39] Esteve J, Villamor N, Colomer D, et al. Stem cell transplantation for chronic lymphocytic leukemia: different outcome after autologous and allogeneic transplantation and correlation with minimal residual disease status. Leukemia 2001;15(3):445-51.

[40] Moreno C, Villamor N, Colomer D, et al. Clinical significance of minimal residual disease, as assessed by different techniques, after stem cell transplantation for chronic lymphocytic leukemia. Blood 2006;107(11):4563-9.

[41] Dreger P, Stilgenbauer S, Benner A, et al. The prognostic impact of autologous stem cell transplantation in patients with chronic lymphocytic leukemia: a risk-matched analysis based on the VH gene mutational status. Blood 2004;103(7):2850-8.

[42] Sutton L, Chevret S, Tournilhac O, et al. Autologous stem cell transplantation as a first-line treatment strategy for chronic lymphocytic leukemia: a multicenter, randomized, controlled trial from the SFGM-TC and GFLLC. Blood 2011;117(23):6109-19.

[43] Brion A, Mahe B, Kolb B, et al. Autologous transplantation in CLL patients with B and C Binet stages: final results of the prospective randomized GOELAMS LLC 98 trial. Bone marrow transplantation 2011;47(4):542-8.

[44] Michallet M, Chevret S, R B. Comparative study between autologous or allogenic transplantations and conventional chemotherapy in chronic lymphocytic leukemia (CLL): A European Blood and Marrow Transplantation (EBMT) and French CLL Cooperative Group Study [abstract].. Bone marrow transplantation 2003.

[45] Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modi‐ fied T cells in chronic lymphoid leukemia. The New England journal of medicine 2011;365(8):725-33.

[46] Gribben JG, Zahrieh D, Stephans K, et al. Autologous and allogeneic stem cell trans‐ plantations for poor-risk chronic lymphocytic leukemia. Blood 2005;106(13):4389-96.

[47] Montserrat E, Moreno C, Esteve J, Urbano-Ispizua A, Gine E, Bosch F. How I treat refractory CLL. Blood 2006;107(4):1276-83.

[48] Doney KC, Chauncey T, Appelbaum FR. Allogeneic related donor hematopoietic stem cell transplantation for treatment of chronic lymphocytic leukemia. Bone mar‐ row transplantation 2002;29(10):817-23.

[49] Esteve J, Bosch F, C M. Prolonged response after allogeneic stem-cell transplantation (alloSCT) for high-risk chronic lymphoblastic leukemia (CLL): long term outcome of a series from a single institution [abstract].. Haematologica 2005;90((suppl 2)):41.

[50] Kharfan-Dabaja MA, Kumar A, Behera M, Djulbegovic B. Systematic review of high dose chemotherapy and autologous haematopoietic stem cell transplantation for chronic lymphocytic leukaemia: what is the published evidence? British journal of haematology 2007;139(2):234-42.

[51] Michallet M, Michallet AS, QH L. Conventional HLA-Identical Sibling Bone Marrow Transplantation is Able To Cure Chronic Lymphocytic Leukemia. A Study from the EBMTand IBMT Registries [abstract]. Blood 2003:102.

[52] Horowitz M, Montserrat E, K S. Haematopoietic stem cell transplantation for chronic lymphocytic leukemia [abstract]. Blood 2000:96.

[53] Khouri IF, Keating MJ, Saliba RM, Champlin RE. Long-term follow-up of patients with CLL treated with allogeneic hematopoietic transplantation. Cytotherapy 2002;4(3):217-21.

[54] Pavletic ZS, Arrowsmith ER, Bierman PJ, et al. Outcome of allogeneic stem cell trans‐ plantation for B cell chronic lymphocytic leukemia. Bone marrow transplantation 2000;25(7):717-22.

[55] Toze CL, Galal A, Barnett MJ, et al. Myeloablative allografting for chronic lympho‐ cytic leukemia: evidence for a potent graft-versus-leukemia effect associated with graft-versus-host disease. Bone marrow transplantation 2005;36(9):825-30.

[56] Moreno C, Villamor N, Colomer D, et al. Allogeneic stem-cell transplantation may overcome the adverse prognosis of unmutated VH gene in patients with chronic lymphocytic leukemia. J Clin Oncol 2005;23(15):3433-8.

[57] Caballero D, Garcia-Marco JA, Martino R, et al. Allogeneic transplant with reduced intensity conditioning regimens may overcome the poor prognosis of B-cell chronic lymphocytic leukemia with unmutated immunoglobulin variable heavy-chain gene

and chromosomal abnormalities (11q- and 17p-). Clin Cancer Res 2005;11(21): 7757-63.

[58] Rawstron A, Hillmen P, Houlston R. Clonal lymphocytes in persons without known chronic lymphocytic leukemia (CLL): implications of recent findings in family members of CLL patients. Seminars in hematology 2004;41(3):192-200.

[59] Khouri IF, Przepiorka D, van Besien K, et al. Allogeneic blood or marrow transplantation for chronic lymphocytic leukaemia: timing of transplantation and potential effect of fludarabine on acute graft-versus-host disease. British journal of haematology 1997;97(2):466-73.

[60] Michallet M, Archimbaud E, Bandini G, et al. HLA-identical sibling bone marrow transplantation in younger patients with chronic lymphocytic leukemia. European Group for Blood and Marrow Transplantation and the International Bone Marrow Transplant Registry. Annals of internal medicine 1996;124(3):311-5.

[61] Khouri I, Champlin R. Allogenic bone marrow transplantation in chronic lymphocytic leukemia. Annals of internal medicine 1996;125(9):780.

[62] Fraser CJ, Bhatia S, Ness K, et al. Impact of chronic graft-versus-host disease on the health status of hematopoietic cell transplantation survivors: a report from the Bone Marrow Transplant Survivor Study. Blood 2006;108(8):2867-73.

[63] Sorror ML, Storer BE, Sandmaier BM, et al. Five-year follow-up of patients with advanced chronic lymphocytic leukemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol 2008;26(30): 4912-20.

[64] Sorror ML, Maris MB, Sandmaier BM, et al. Hematopoietic cell transplantation after nonmyeloablative conditioning for advanced chronic lymphocytic leukemia. J Clin Oncol 2005;23(16):3819-29.

[65] Delgado J, Pillai S, Benjamin R, et al. The effect of in vivo T cell depletion with alemtuzumab on reduced-intensity allogeneic hematopoietic cell transplantation for chronic lymphocytic leukemia. Biol Blood Marrow Transplant 2008;14(11):1288-97.

[66] Oscier D, Fegan C, Hillmen P, et al. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. British journal of haematology 2004;125(3):294-317.

[67] Keating MJ, O'Brien S, Kontoyiannis D, et al. Results of first salvage therapy for patients refractory to a fludarabine regimen in chronic lymphocytic leukemia. Leukemia & lymphoma 2002;43(9):1755-62.

[68] Khouri IF, Saliba RM, Admirand J, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. British journal of haematology 2007;137(4):355-63.

[69] Perkins JG, Flynn JM, Howard RS, Byrd JC. Frequency and type of serious infections in fludarabine-refractory B-cell chronic lymphocytic leukemia and small lymphocytic

lymphoma: implications for clinical trials in this patient population. Cancer 2002;94(7):2033-9.

[70] Pavletic SZ, Khouri IF, Haagenson M, et al. Unrelated donor marrow transplantation for B-cell chronic lymphocytic leukemia after using myeloablative conditioning: results from the Center for International Blood and Marrow Transplant research. J Clin Oncol 2005;23(24):5788-94.

[71] Dreger P, Stilgenbauer S, Buttcher S, et al. Prognostic factors for outcome of nonmyeloablative allogeneic stem cell transplantation (NST) in poor-risk chronic lymphocytic leukemia (CLL): final results from a prospective multicenter trial (GCLLSG CLL3X study) [abstract]. Blood 2008:112: 212.

[72] Kolb HJ, Mittermuller J, Clemm C, et al. Donor leukocyte transfusions for treatment of recurrent chronic myelogenous leukemia in marrow transplant patients. Blood 1990;76(12):2462-5.

[73] Slavin S, Naparstek E, Nagler A, Ackerstein A, Kapelushnik J, Or R. Allogeneic cell therapy for relapsed leukemia after bone marrow transplantation with donor peripheral blood lymphocytes. Experimental hematology 1995;23(14):1553-62.

[74] Dreger P, Brand R, Hansz J, et al. Treatment-related mortality and graft-versus-leukemia activity after allogeneic stem cell transplantation for chronic lymphocytic leukemia using intensity-reduced conditioning. Leukemia 2003;17(5):841-8.

[75] Schetelig J, Thiede C, Bornhauser M, et al. Evidence of a graft-versus-leukemia effect in chronic lymphocytic leukemia after reduced-intensity conditioning and allogeneic stem-cell transplantation: the Cooperative German Transplant Study Group. J Clin Oncol 2003;21(14):2747-53.

[76] Dreger P, Brand R, Milligan D, et al. Reduced-intensity conditioning lowers treatment-related mortality of allogeneic stem cell transplantation for chronic lymphocytic leukemia: a population-matched analysis. Leukemia 2005;19(6):1029-33.

[77] Ritgen M, Bottcher S, Stilgenbauer S, et al. Quantitative MRD monitoring identifies distinct GVL response patterns after allogeneic stem cell transplantation for chronic lymphocytic leukemia: results from the GCLLSG CLL3X trial. Leukemia 2008;22(7): 1377-86.

[78] Farina L, Carniti C, Dodero A, et al. Qualitative and quantitative polymerase chain reaction monitoring of minimal residual disease in relapsed chronic lymphocytic leukemia: early assessment can predict long-term outcome after reduced intensity allogeneic transplantation. Haematologica 2009;94(5):654-62.

[79] Schetelig J, van Biezen A, Brand R, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17p deletion: a retrospective European Group for Blood and Marrow Transplantation analysis. J Clin Oncol 2008;26(31):5094-100.

[80] Hoogendoorn M, Jedema I, Barge RM, et al. Characterization of graft-versus-leuke‐
mia responses in patients treated for advanced chronic lymphocytic leukemia with
donor lymphocyte infusions after in vitro T-cell depleted allogeneic stem cell trans‐
plantation following reduced-intensity conditioning. Leukemia 2007;21(12):2569-74.

[81] Malhotra P, Hogan WJ, Litzow MR, et al. Long-term outcome of allogeneic stem cell
transplantation in chronic lymphocytic leukemia: analysis after a minimum follow-
up of 5 years. Leukemia & lymphoma 2008;49(9):1724-30.

[82] Tam CS, O'Brien S, Lerner S, et al. The natural history of fludarabine-refractory
chronic lymphocytic leukemia patients who fail alemtuzumab or have bulky lym‐
phadenopathy. Leukemia & lymphoma 2007;48(10):1931-9.

[83] Bottcher S, Ritgen M, Dreger P. Allogeneic stem cell transplantation for chronic lym‐
phocytic leukemia: lessons to be learned from minimal residual disease studies.
Blood reviews 2011;25(2):91-6.

[84] Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine
and cyclophosphamide in patients with chronic lymphocytic leukaemia: a rando‐
mised, open-label, phase 3 trial. Lancet 2010;376(9747):1164-74.

[85] Delgado J, Thomson K, Russell N, et al. Results of alemtuzumab-based reduced-in‐
tensity allogeneic transplantation for chronic lymphocytic leukemia: a British Society
of Blood and Marrow Transplantation Study. Blood 2006;107(4):1724-30.